THE CONSTITUTION OF THE HEREDITARY MATERIAL.

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There are two ways in which the relation of the egg to the characters of the individual that develops from the egg has been interpreted.

1. The egg has been thought of as a whole and the characters of the individual as the product of its activity as a unit.

2. The egg has been thought of as made up of representative particles of some sort that stand in a definite relation to the parts of the individual that comes from the egg.

Weismann, whose speculations occupied the forefront of interest at the close of the last century, adopted the latter view; namely, that the germ is made up of particles, which he called determiners. For Weismann embryonic development became merely the sorting out of the particles of the germ to their respective parts of the embryo. Each region of the body owed its peculiarities to the particles that came to it by this sorting-out process. In fact, one may go so far, I think, as to say that Weismann borrowed from Roux this particular form of the preformation in order to give a formal explanation of *embryonic differentiation.* But Weismann's theory soon encountered three serious reverses.

In the first place, the study of the minute structure and behavior of the segmenting egg shows no evidence that any such sorting-out process takes place, as Weismann postulated. It has been shown that the chromosomes divide equally at every division, and that every cell of the body contains the entire complex that was present in the fertilized egg-cell itself.

In the second place, it was shown that the sequence of the cleavage planes of the egg could be artificially altered, yet a normal embryo develop.

In the third place, it was shown that in some eggs each of the first two, or first four cells derived from the egg is capable of forming a whole embryo. This result creates a strong presumption against the adequacy of Weismann's interpretation of development.

Meanwhile one of the greatest biological discoveries of the last century—one that had a very direct bearing on the traditional interpretations of predetermination—was forgotten. I refer to Mendel's work. Mendel showed that when two related organisms, differing from each other in a single character, are crossed, and their offspring are again bred together, that in the second generation individuals appear that are like their grandparents. He showed that the numerical proportions, in which they appear, could be explained on the assumption of one factor difference between the original forms. This result might be interpreted to mean either that the two original germ cells, taken as a whole, represent such a factor difference; or it might be interpreted to mean that the original germ cells had one particulate difference. But Mendel went further, and showed that when two related organisms that differ in two, or three, or more different characters are bred to each other, all possible combinations of the original characters appear later. It might seem then that we must abandon the view that each germ cell is to be thought of as a whole, for we see that the parts of each can be separated to become parts of others. In this sense Mendel's results seem to furnish a brilliant confirmation of Weismann's theory, in so far as it relates to preformation in the germ, and in the last edition of his "Vorträge ueber Descendenz Theorie," Weismann put in his claim to this verification.

In fact, Mendel's discovery does furnish a strong argument in favor of that part of Weismann's view that deals with the constitution of the germ-plasm, but it by no means confirms that part of Weismann's theory which postulates that embryonic development is a sorting-out process of representative particles.

Let us turn our attention, then, to Mendel's law and examine in how far it justifies an assumption that there are specific substances in the germ cells.

Mendel's law postulates that the early germ cells (and it may be added all of the body cells too) contain two of each kind of the

hereditary factors,—one derived from each of its parents. Mendel's law postulates further, that, in the ripening of the germ cells, the members of each pair separate (Fig. 1). Each mature germ cell comes to contain but a single element (or factor) of each kind.

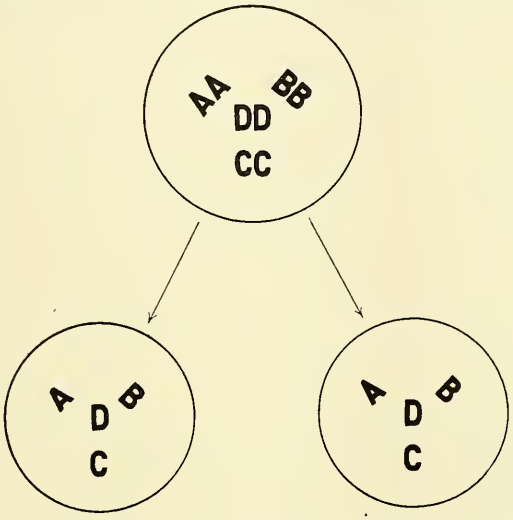

Fig. 1. Diagram to illustrate segregation of factors. The four pairs of factors represented in the upper circle by AA, BB, CC, DD, undergo segregation so that each germ cell comes to contain one member of each pair.

Now students of cytology had quite independently come to this same conclusion in regard to the germ cells. They had found that each cell contains a definite number of chromosomes, and that there are two of each kind of chromosomes in every cell,—one from each parent (Fig. 2, *a*). It had been found that at the ripening of the germ cells the members of each pair of chromosomes conjugate (Fig. 2, *b*), and then separate from each other (Fig. 2, *c*), so that each mature germ cell comes to contain but a single set of chromosomes (Fig. 2, *d*). Furthermore, students of experimental embryology had obtained independent evidence pointing to the chromosomes as the bearers of the hereditary materials.

We find, then, that cytologists had discovered a mechanism in the cell that they had reason to think was the bearer of the hereditary materials, and that the mechanism fulfills the essential

requirements of Mendel's postulates. There were two further steps necessary to bring the two lines of inquiry into complete accord; namely, (1) correspondence between the number of the chromosomes and the groups of inherited characters, and (2) the interchange between the members of the same pair of chromosome.

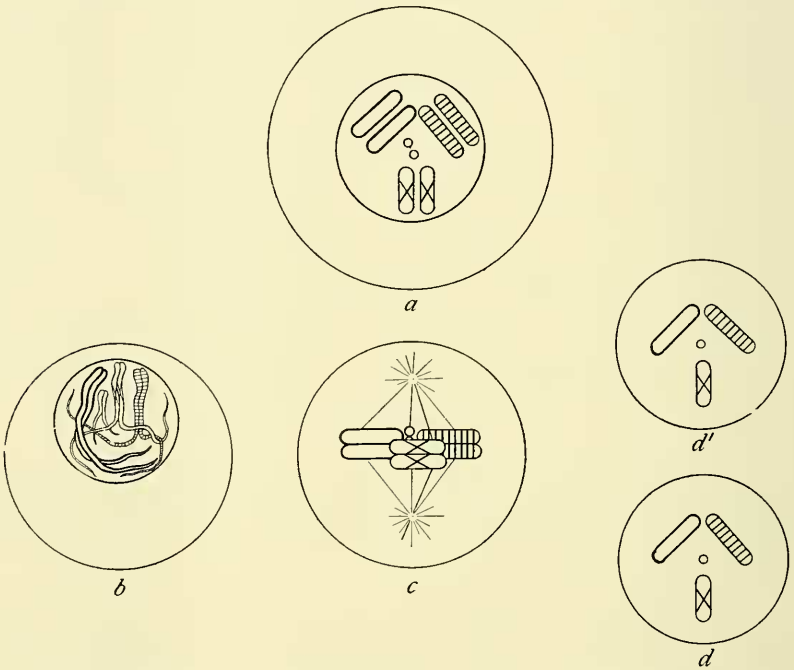

FIG. 2. Diagram to illustrate segregation of chromosomes. The four pairs of chromosomes in the upper circle (*a*), conjugate in (*b*) (synopsis stage), prepare for separation in (*c*) and undergo segregation so that each germ cell (d, d′) comes to contain one member of each pair.

The number of chromosomes is small in comparison with the large number of different characters that an animal or a plant possesses. We should expect therefore if in any animal or plant a sufficient number of character-differences were known that the characters would be found to be inherited in groups, and that the number of such groups should be the number of chromosome pairs that such an animal or plant possesses. In very few cases have enough characters been found to make such a comparison of any value.

But in the fruit fly, *Drosophila,* that has been intensively studied for five years, over a hundred new, and inherited characters have appeared. They fall into four great groups. A partial list of the four groups is as follows:

GROUP I.

Name.	Region Affected.
Abnormal	Abdomen
Bar	Eye
Bifid	Venation
Bow	Wing
Cherry	Eye color
Chrome	Body color
Cleft	Venation
Club	Wing
Depressed	Wing
Dotted	Thorax
Eosin	Eye color
Facet	Ommatidia
Forked	Spines
Furrowed	Eye
Fused	Venation
Green	Body color
Jaunty	Wing
Lemon	Body color
Lethals, 13	Die
Miniature	Wing
Notch	Venation
Reduplicated	Eye color
Ruby	Legs
Rudimentary	Wings
Sable	Body color
Shifted	Venation
Short	Wing
Skee	Wing
Spoon	Wing
Spot	Body color
Tan	Antenna
Truncate	Wing
Vermilion	Eye color
White	Eye color
Yellow	Body color

GROUP II.

Name.	Region Affected.
Antlered	Wing
Apterous	Wing
Arc	Wing
Balloon	Venation
Black	Body color
Blistered	Wing
Comma	Thorax mark
Confluent	Venation
Cream II	Eye color
Curved	Wing
Dachs	Legs
Extra vein.	Venation
Fringed	Wing
Jaunty	Wing
Limited	Abdominal band
Little crossover	II chromosome
Morula	Ommatidia
Olive	Body color
Plexus	Venation
Purple	Eye color
Speck	Thorax mark
Strap	Wing
Streak	Pattern
Trefoil	Pattern
Truncate	Wing
Vestigial	Wing

GROUP III.

Name.	Region Affected.
Band	Pattern
Beaded	Wing
Cream III	Eye color
Deformed	Eye
Dwarf	Size of body
Ebony	Body color
Giant	Size of body
Kidney	Eye
Low crossingover	III chromosome
Maroon	Eye color
Peach	Eye color

GROUP IV.

Name.	Region Affected.
Bent	Wing
Eyeless	Eye

GROUP III.—*Continued.*

Name.	Region Affected.
Pink	Eye color
Rough	Eye
Safranin	Eye color
Sepia	Eye color
Sooty	Body color
Spineless	Spines
Spread	Wing
Trident	Pattern
Truncate intensf.	Wing
Whitehead	Pattern
White ocelli	Simple eye

The four pairs of chromosomes of *Drosophila* are shown in the next diagram, Fig. 3.

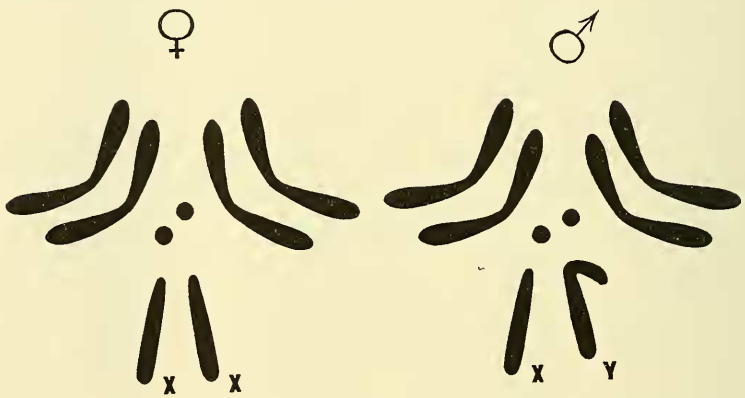

FIG. 3. Diagram of the four pairs of chromosomes of Drosophila ampelophila; to the left the chromosomes of the female; to the right those of the male.

The correspondence between the four character groups and the four pairs of chromosomes is obvious even to the size relations. This relation, or correspondence, does not however tell us anything in respect to the way in which the chromosomes stand for the characters of the group. So far, the result only shows that the characters of a given group are in some way represented in a particular chromosome. Our work has, however, carried us beyond this point. I may illustrate this by an example from the first group, containing sex linked characters. We mean by sex linked characters that they follow the known distribution of the X chromosomes. For in-

stance, the factor that determines the character for white eyes is sex linked, as is also the factor that determines the character for miniature wings. If we cross a female with white eyes and miniature wings to a male with red eyes and long wings, the sons will have white eyes and miniature wings. The explanation of this result is found in the distribution of the chromosomes. The sons get their single X chromosomes from their mother. Hence they show the characters that this chromosome carried in the mother, who had white eyes and miniature wings. The daughters, however, get one of their X chromosomes from their father through his female producing sperm. This chromosome carried a factor for red eyes and another for long wings, which factors dominate those carried by the other X chromosome that the daughters get from their mother, namely, the factors for white eyes and for miniature wings. These relations are shown in Fig. 4.

If these daughters and sons are bred to each other they produce four kinds of individuals, viz., red long, white miniature, red miniature, and white long. These are the four classes that Mendel's law calls for, but they do not occur in the Mendelian proportion (9:3::3:1) when two pairs of factors, as here, are involved. The reason for this is two-fold. In the first place the female alone carries two X chromosomes. The male carries but one. Hence there is an unequal distribution of the X chromosomes in the spermatozoa, for, only half of them can get an X chromosome. These are the female-producing spermatozoa. The result is, as has been shown, that in the first generation the sons inherit their single X chromosome from their mother and none of the dominant characters of the father. Since in this case the sons carry no dominant factor either in their X bearing (female producing), or in their Y bearing (male producing sperm), the second generation here reveals completely the composition of the egg cells that the F_1 female carries.

On Mendel's law of random assortment of two pairs of factors we should expect the four classes that here appear in the second generation to be equal in number. On the contrary we find that two of them are twice as numerous as the other two. On inspection we see that the two larger classes are white miniature and red

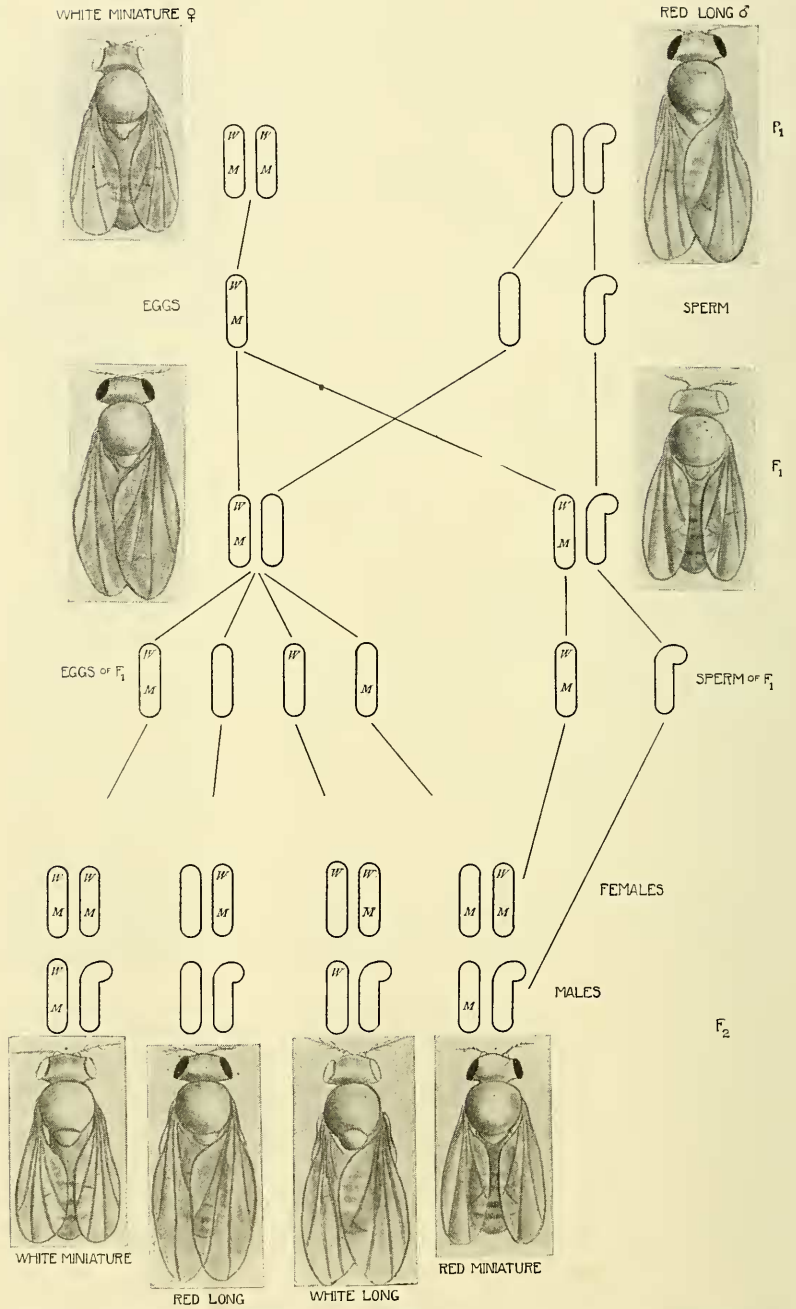

FIG. 4. Diagram to show the inheritance of two pairs of recessive sex linked characters, viz. white eyes (W) and miniature wings (M). The normal, dominant allelomorphs of these factors are omitted.

long. These correspond to the two grandparents. The two smaller classes are white long and red miniature.

We can account for this result if we assume first that the two factors that went in together in the same chromosome tend to hold together. This would account for the two larger classes. Second that the two smaller classes are due to interchanges between the two X chromosomes. Such interchange would here take place only once in three times.

We can test this conclusion by planning the experiment in such a way that white and miniature now go in from opposite sides,—white from one parent, and miniature from the other. When we do this we find that the large classes in the second (back cross) generation will be red miniature and white long and that the small classes will now be red long and white miniature. The ratio of the large to the small classes will be exactly the same as in the first case. In other words the interchange between the X chromosomes is the same regardless of what factors each contains.

If one admits that the chromosomes are the bearers of the hereditary factors he is forced to admit that experiments like these prove that somehow interchange of factors in homologous chromosomes must occur.

If one thinks of the factors as lying in a linear series in the chromosome (and there is certain evidence that I can not consider here that makes this view imperative) then the chance of a crossing over taking place somewhere in the region between two pairs of factors would be greater the farther apart the factors lie. The percentage of times that crossing over takes place becomes then a measure of the distance apart of the factors in question. If we make this assumption we find that we can give a consistent explanation of everything that we have found in the inheritance of linked factors in *Drosophila*. Not only this, but a far more important fact comes to light. If we determine, on the aforesaid basis, the relation to each other of all the known factors in each of the four groups, then, when a new factor appears, we need only determine its group and its relation to two factors in that group. With this information we can predict its relation to all other members of that group. In other words we can predict what the numerical relation

will be in the second generation. There is no other way as yet discovered by means of which this relation can be predicted.

If we compare our conception of the structure of the germ plasm with that of Weismann we find in all of his writings except the last one, that he supposed the chromosomes to be alike and that each consisted of a series of ids that contained the totality of the determiners that influence development.

It is true that in his last writing he partially abandons his earlier idea of *whole ids* for a conception nearer to ours of *partial ids,*—at least for some of the determiners. In this respect his view more nearly approaches the one here maintained. But even then his view not being based on numerical data would leave us entirely helpless in explaining the phenomena of inheritance in any particular case. Without wishing in the least to detract from the value of Weismann's brilliant speculation, nevertheless the difference in the way in which the conclusions were reached in the two cases is one of fundamental significance in all scientific work. Our view is based on accurate numerical data that enables us to predict what any given result in this field will be. It is this power to predict that gives significance to a scientific theory. In this regard we believe that our interpretation is a long step in advance of the purely imaginative conception of the germ plasm that Weismann advanced.

If now we bring our conception of the germ plasm to bear on the problem of development we have a very different view point of that process from the one Weismann pictured.

We think of every cell in the body containing one set of chromosomes received from the mother plus one set from the father. The materials carried by these chromosomes influence development in their entirety. Although we are able to localize certain materials in the chromosomes that when present cause the eyes to be white, and others that cause the eyes to be red, we do not mean that these materials in the chromosomes go directly only to the parts that show their influence more markedly. We mean that given one kind of material and the rest of the cell there is elaborated a white eye; given a different material in the same locus it produces, in conjunction with the rest of the cell, a red eye.

To say that the germinal material that makes a white eye is different from the germinal material that makes a red eye is a platitude. But to be able to locate a particular material in the one case *in relation to other materials* is a very different matter, because by means of this information we are able to explain the results on a mechanistic basis, and are able to predict the results of untried combinations. Without this information the prediction would be impossible.

We are led then to a third conception of predetermination. It is this! That while the hereditary material is made up of different discrete and separable particles (chemical substances) that have a definite position in the chromosomes, the effects of each of these particles must be supposed to be produced in combination with many, or even with all other parts of the cells in which they are contained.

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